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Roles of Glucagon and Insulin in the Regulation of Metabolism in Ruminants – A Review

R. P. BROCKMAN*

INTRODUCTION

Metabolic diseases tend to be due to inadequacy of enzymes. However, the activation of these enzymes is at least partially dependent upon hormonal balance. Thus, an understanding of the roles of hormones in regulating metabolism is essential to an appreciation of the pathophysiology of metabolic disorders.

Intermediary metabolism in ruminant animals differs from that of nonruminant animals in several fundamental respects. As a result of microbial activity in the rumen most of the dietary carbohydrate is fermented to short chain volatile fatty acids (VFA) (2). As little dietary carbohydrate is absorbed as hexose sugar (16, 53) glucose needs must be met by glucose synthesis from noncarbohydrate sources, that is, gluconeogenesis. Since their glucose requirements are similar to that in postabsorptive nonruminant animals (7), gluconeogenesis is of major importance. In ruminant animals hepatic glucose output (primarily gluconeogenesis) is greatest in the fed (postabsorptive) animal (18), whereas in nonruminants (68) gluconeogenesis is greatest during starvation.

A second major difference concerns lipid metabolism. Acetate, instead of glucose, is the major substrate for lipogenesis in ruminants (7, 43). This means that ruminant gluconeogenesis and lipogenesis are maximal at the same time, while in nonruminants gluconeogenesis is greatest when lipolysis is greatest. Since the major substrates for lipogenesis and gluconeogenesis are absorbed from the gastrointestinal tract, substrate supply may play a major role in the regulation of these processes. However, changes in hormonal concentrations undoubtedly are important as well. The hormonal influences may be 1) indirect, by regulating substrate supply by effects at extra-hepatic sites or 2) direct, by influencing adipose tissue lipogenesis and/or hepatic gluconeogenesis. This review is concerned with the roles of the pancreatic hormones, glucagon and insulin, in the regulation of intermediary metabolism in ruminants.

Glucagon is a hyperglycemic hormone, capable of promoting gluconeogenesis and lipolysis. Insulin has a hypoglycemic effect and promotes storage of metabolites in peripheral tissues. On a minute-to-minute basis these hormones regulate blood glucose concentrations and direct the movement of glucose, amino acids and possibly volatile fatty acids (VFA) between the liver and peripheral tissues. On a long term basis, glucagon may be considered catabolic and insulin anabolic. Therefore, the regulation of metabolism by insulin and glucagon is concerned with storing excess energy during feasting and using it during starvation to sustain life.

In ruminants, the major glucogenic substrates are propionate, lactate/pyruvate, amino acids and glycerol (16). In the fed animal, absorbed propionate and amino acids are the major glucose precursors. However, during starvation the major precursors must be supplied by peripheral stores. Since lipid stores provide only a small amount of substrate as glycerol (glucose derived from glycerol is about 15% [19]), amino acids and, hence peripheral protein, must be the major substrates for gluconeogenesis during starvation. Therefore, a balance must be maintained in order to avoid excessive gluconeogenesis at the expense of peripheral protein by sparing glucose utilization. Part of this is the utilization of lipid stores as an energy source instead of glucose (49).

INSULIN – THE STORAGE HORMONE

Glucose

Insulin is the hormone which promotes storage of metabolic fuels within cells. Insulin increases the movement of glucose into many peripheral

*Department of Veterinary Physiological Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0.

TABLE I

GLYCEMIA, PRODUCTION AND REMOVAL RATES OF GLUCOSE AND PLASMA GLUCAGON CONCENTRATIONS IN 55 KG SHEEP BEFORE AND DURING TWO HOUR INSULIN INFUSIONS (1.2 U/HR) WITHOUT AND WITH GLUCOSE (12 MMOL/HR). VALUES ARE MEANS ± S.E.[a]

		Infusion (Hours)		
	Pre-infusion	0–0.5	0.5–1	1–2
Insulin Infusion (n = 5)				
Glycemia (mmol/l)	2.61±0.05	2.33±0.08[c]	2.00±0.06[c]	1.88±0.10[c]
Glucose Prod. (mmol/hr)	26.8±1.2	23.4±1.6[c]	22.9±0.9[c]	27.3±1.6
Glucose Rem. (mmol/hr)	26.8±1.2	30.8±1.7[c]	27.8±1.8	27.4±1.4
Glucagon (pg/ml)	240±40	536±62[c]	437±51[c]	407±69
Insulin and Glucose Infusion (n = 3)				
Glycemia (mmol/l)	2.36±0.28	2.65±0.26	2.57±0.12	2.31±0.10
Glucose Prod. (mmol/hr)	25.1±2.4	34.7±3.1[c]	34.2±3.3[c]	34.0±2.7[c]
End. Production[b] (mmol/hr)	25.1±2.4	22.6±2.8	22.1±2.8[c]	21.9±2.0[c]
Glucose Rem. (mmol/hr)	25.1±2.4	29.0±3.0[c]	35.4±2.9[c]	36.2±2.8[c]
Glucagon (pg/ml)	240±15	267±25	237±33	248±15

[a]Unpublished data, R. P. Brockman. Glucose production and removal was determined by primed-continuous infusion of [6-^{3}H]glucose.

[b]Endogenous production is glucose production minus rate of infusion of exogenous glucose.

[c]Significantly different from corresponding control, $P < 0.05$, paired t-test.

tissues (26, 27, 73) including both muscle (48) and fat (51). However, the response to insulin seems to be slower in ruminants than in nonruminants (48).

In the removal of a large glucose load, the role of insulin is directed primarily at peripheral tissues. Since the ruminant liver is capable of taking up only a small amount of glucose from blood (5), hepatic effects of insulin would be less dramatic than in nonruminants. *In vivo* studies in sheep indicate that insulin can inhibit glucose production only 15% (35, 73). Unpublished data (Table I) further show that when hypoglycemia occurs the compensatory glucagon secretion is associated with a return of glucose production to normal. If the hypoglycemia and concomitant hyperglucagonemia is prevented by infusing glucose at a low rate with insulin, glucose production, nevertheless, is still only inhibited about 15%. This inhibition of glucose production may be inhibition of glycogenolysis, not gluconeogenesis. Unpublished observations from this laboratory (Table II) indicate insulin does not significantly inhibit incorporation of the label from [U-^{14}C]alanine into glucose. Perhaps, since in these experiments the sheep were fed a maintenance diet, the basal rate of gluconeogenesis was too low to be inhibited by insulin. In any case, these data suggest that insulin has greater effects on the disposal of glucose at nonhepatic sites than on hepatic output of glucose.

Lipid

The effect of insulin on lipid storage is less clear. *In vitro* studies show little (74) or no effect (57) on lipolysis or lipogenesis. Yang and Baldwin (74) reported that insulin enhances the incorporation of ^{14}C from glucose into lipid in the presence of acetate and also increases the incorporation of acetate into lipid by about 50%. In addition, insulin inhibits epinephrine-enhanced lipolysis *in vitro* (75). Ruminant adipose tissue does not appear as responsive to insulin as rat tissue in *in vitro* studies (52). In contrast, in *in vivo* studies insulin administration is associated with reduction in plasma concentrations of glycerol (15) and free fatty acids (73) and with a decrease in net output of glycerol (34) and free fatty acids (51) from ovine adipose tissue. Furthermore, the uptake of acetate by peripheral tissue, the major substrate for lipogenesis (43), is restored to normal by insulin treatment in alloxan-diabetic sheep (48). Jarrett *et al* (48) have shown that insulin decreases the half-life of exogenous acetate in

TABLE II

PLASMA ALANINE CONCENTRATION, WHOLE BODY PRODUCTION AND CONVERSION TO GLUCOSE BEFORE AND DURING INSULIN (1.2 U/HR) PLUS GLUCOSE (12 MMOL/HR) INFUSIONS IN THREE SHEEP WEIGHING 55 KG.[a] VALUES ARE MEANS ± S.E.

	Conc Ala μM	Prod Ala mmol/hr	Ala → Gluc[b] mmol/hr
Control	102±5	11.1±0.8	1.09±0.03
Infusion[c]	90±6[d]	12.5±1.3	1.04±0.06

[a]Unpublished data, R. P. Brockman. It was obtained by simultaneous infusion of [U-^{14}C]-alanine and [6-^{3}H]glucose as described in reference 30. The infusion of glucose with insulin prevented hypoglycemia normally seen with insulin infusion. Corresponding glucose data is presented in Table I.

[b]Mmol of alanine used to synthesize glucose.

[c]Infusion period was two hours.

[d]Significantly different from corresponding control, $P < 0.05$, paired t-test.

alloxan-diabetic sheep. A decrease in plasma acetate concentration following insulin administration in normal sheep (36, 58) is consistent with a stimulatory effect on acetate utilization. Thus, *in vivo* studies support a role for insulin in promoting net lipogenesis in nonhepatic tissues. Nevertheless, glucose itself is a greater stimulus for lipogenesis than insulin *in vitro* (52, 74).

Protein

Insulin has a hypoamino acidemic effect in many species including ruminants (34, 36). Studies with isotopically labelled amino acids indicate this is associated with an enhancement of incorporation of amino acids into muscle protein (50). An insulin-enhanced uptake of amino acids by muscle is supported by two studies in sheep. Glucose infusions, which stimulate insulin secretion, are associated with increased uptake of amino acids across the hind limbs (61). In contrast, during starvation, when insulin concentrations are low (69), the hind limbs release amino acids compared to a slight uptake in the fed state (6). Furthermore, the hypoamino acidemic effect of insulin is not accounted for by hepatic effects. When insulin and insulin plus glucose are infused *in vivo* (34) no effect on net hepatic uptake of amino acids is attributable to insulin. This is similar to results from *in vivo* studies in rats (66) where insulin administration is associated with enhanced movement of labelled amino acid into muscle but not liver when hypoglycemia is prevented. A lack of effect of insulin on net hepatic uptake is consistent with no effect of insulin on hepatic gluconeogenesis from alanine in sheep fed a maintenance diet (Table II).

Insulin, it appears, directs its influences on metabolism primarily at nonhepatic sites. It directs the movement of certain metabolites into muscle and adipose tissue. In its absence, synthetic activity is reduced in these tissues and there is a net movement of metabolites from them to the liver.

GLUCAGON – ENERGY MOBILIZING HORMONE

As in other species, glucagon is a potent hyperglycemic hormone in ruminants. It stimulates both glycogenolysis and gluconeogenesis in sheep (30). Furthermore, a reduction in glucagon concentration brings a 15–20% reduction in glucose production in sheep (31). Glucagon-enhanced gluconeogenesis is associated with increased activity of hepatic pyruvate carboxylase (32), a key gluconeogenic enzyme, as well as augmented hepatic extraction of gluconeogenic substrates, such as alanine, pyruvate/lactate and glutamine, but not glycerol (34). Since the adenylate system seems to mediate the hepatic effects of glucagon (40), observations that dibutyryl cyclic adenosine monophosphate stimulates gluconeogenesis from pyruvate in bovine liver slices (3) is consistent with a glucagon effect on gluconeogenesis. Other *in vitro* studies indicate glucagon may enhance the conversion of propionate to glucose (37, 67). However, concentrations of glucagon used in these *in vitro* studies were well above physiological ranges.

An effect of glucagon on ruminant adipose tissue metabolism is equivocal. Glucagon infusions *in vivo* have increased plasma fatty acid (8) and glycerol (28, 34) concentrations if glucagon-stimulated insulin secretion is prevented. This suggests that if glucagon has an effect on adipose tissue, it is not as potent as insulin. *In vitro* studies have not confirmed a lipolytic role for glucagon in ruminants (14). In contrast, glucagon stimulated lipolysis has been demonstrated in other species (72).

Glucagon seems to have no direct effect on peripheral amino acid metabolism. Studies conducted in man (63) and rats (41) show no effect on venoarterial concentration differences or on accumulation in peripheral tissues. However, glucagon promotes uptake of glucogenic amino acids by liver of sheep *in vivo* (34) and enhances the conversion of alanine to glucose (30). This reduces plasma amino acid concentrations. Thus, less are available for utilization by peripheral tissues.

It appears, then, that glucagon acts primarily on the liver in regulating metabolism. Its role is to promote hepatic glucose output, by both gluconeogenesis and glycogenolysis.

FACTORS INFLUENCING INSULIN AND GLUCAGON SECRETION

Postprandial Effects

In cattle and sheep, plasma insulin (9, 10, 39, 65) and glucagon (9) concentrations have been shown to increase significantly after feeding. The peak levels of these hormones are observed two to four hours after a meal. However, the plasma insulin and glucagon concentrations correlate poorly with changes in blood glucose, despite demonstrated responses to hyperglycemia and hypoglycemia (29), or plasma amino acid concentrations (19). But, they are associated with changes in plasma VFA concentrations (9, 10, 11, 65). In addition, on a variety of diets, the mean level of insulin seems to correlate with the digestible organic matter intake (12, 13).

Volatile Fatty Acids

Intravenous propionate, butyrate and valerate are potent stimulators of insulin (9, 44, 54, 55) and glucagon (9, 54, 55, 62) secretion. Six carbon fatty acids appear to be the most potent fatty acids with respect to stimulating insulin secretion and promoting hyperglycemia. Longer and shorter fatty acids are progressively less effective (1, 62). The situation with acetate is not clear. Whereas

Ambo *et al* (1) and Trenkle (70) report that acetate is a mild promoter of insulin secretion, others (54, 62) report no effect.

The physiological significance of VFA as regulators of insulin secretion is questioned (69). In most studies utilizing intravenous infusions of VFA (1, 9, 39, 44, 54, 69) they have been above physiological entry rates or by unphysiological routes, thus extremely high blood levels of VFA reached the pancreas. However, administration of propionate and butyrate at physiological entry rates (17), via a mesenteric vein catheter, is associated with significant elevations in insulin and glucagon concentrations (R.P. Brockman, unpublished observations). Although 80–90% of the absorbed propionate and butyrate are removed as it passes through the liver (17), plasma VFA concentrations following feeding are elevated significantly with insulin (9, 10, 11, 65) and glucagon (9) concentrations for four hours. In addition, intraruminal administrations of VFA are associated with a brief marginal elevation of glucagon and insulin (9). Intra-abomasal infusions of VFA produce more dramatic elevations of plasma insulin and glucagon. It appears that while VFA are not the only regulators of insulin and glucagon secretion they certainly play a part.

Amino Acids

Infusion of arginine (38, 45, 56), leucine (38), phenylalanine (38) and amino acid mixtures (56, 59) is associated with elevated plasma insulin concentrations. A role for amino acids in regulating insulin secretion is supported by studies (13) where plasma insulin levels correlated with plasma concentrations of branched chain amino acids. Studies in nonruminant animals (64) suggest that amino acids may also be important in influencing glucagon secretion.

Nervous System

The autonomic nervous system has been implicated in secretion of pancreatic hormones. Jarrett and Potter (47) observed that lambs, whose splanchnic nerves were sectioned, are more sensitive to insulin than normal lambs. These results are consistent with this nerve playing a role in the compensatory glucagon response to insulin hypoglycemia (22, 29). The glucagon response to hypoglycemia is delayed in splanchnic nervectomized calves (25). Furthermore, electrical stimulation of the peripheral end of the splanchnic nerve in adrenalectomized sheep increases glucagon and decreases insulin secretion (20, 24). Consistent with these observations are reports that epinephrine stimulates glucagon secretion (9, 62) and inhibits insulin secretion (9, 46). This lends support to a role for these hormones in stress (21). Stimulation of glucagon and inhibition of insulin secretions are associated with stress in sheep (33) and other animals (21).

The parasympathetic system may also be involved in glucagon secretion. Vagotomy impairs the hyperglycemic response to butyrate (60). Atropine administration to calves in which the splanchnic nerves are cut is associated with reduced glucagon concentrations and impaired glucagon responses to hypoglycemia (25). Atropine administration in normal calves is associated with decreased glucagon but not insulin concentrations. That study (25) further suggests that parasympathetic innervation is important in the early response to hypoglycemia whereas the later response is a general stress reaction, a sympathetic response insensitive to glucose. Others have indicated that the parasympathetic system may also be involved in the insulin response to feeding in lambs (12). While atropine does not affect basal levels of insulin (10, 23) it blocks the insulin peak following feeding.

Gastrointestinal Hormones

Other factors which may be important in regulating insulin are gastrointestinal hormones. Studies in goats (4) and sheep (71) have shown that pancreozymin can stimulate insulin release. Trenkle (71) reported that secretin can stimulate insulin secretion. While additional information is lacking for ruminant species, studies in nonruminant animals indicate that gastrin, secretin and pancreozymin stimulate insulin secretion and gastrin and pancreozymin can stimulate glucagon secretion (42). However, gastrin is the only gastrointestinal hormone at physiological concentrations that alters glucagon and/or insulin secretion (42). A role for gastrin is further supported by observations in calves that its concentration increases after eating when insulin and glucagon concentrations also are increased (23). While the effects of gastrointestinal hormones are small, they may play a very important role in modifying the response of insulin and glucagon secretion to other stimuli.

CONCLUSIONS

Insulin appears to be anabolic, promoting the storage of metabolites in peripheral stores. In the absence of insulin, proteolysis and lipolysis is promoted, thus, providing substrate for gluconeogenesis and energy production. Insulin's direct effect on the liver, particularly glucose production, appears to be marginal in ruminants. Insulin's inhibition of gluconeogenesis appears to depend upon substrate availability. On the other hand, glucagon is catabolic. While it has no direct effect on peripheral protein stores, it appears to be lipolytic. More importantly, however, it enhances the hepatic removal of certain glucose precursors and stimulates gluconeogenesis. The net effect of glucagon is to promote gluconeogenesis at the expense of peripheral stores.

The secretion of glucagon and insulin can be influenced by glucose, certain amino acids, VFA,

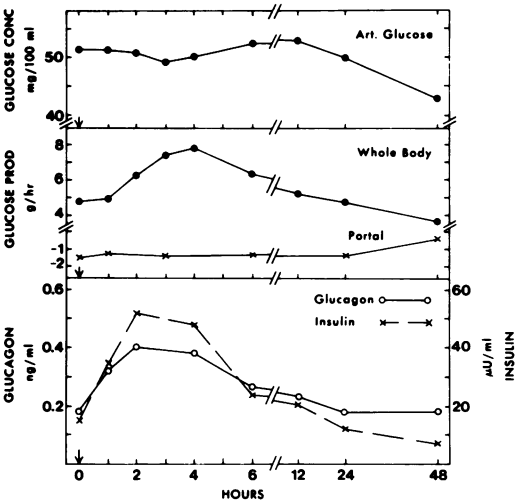

FIGURE 1. Relationship of plasma glucagon and insulin and blood glucose concentrations and whole body and net portal glucose productions in 55 kg sheep to feeding. Sheep were fed at zero hour. Glucose production is greatest when glucagon concentrations are highest. This figure is adapted from data presented in references 9, 10, 18 and 53.

nervous stimulation, adrenal medullary hormones and gastrointestinal hormones. This allows the alteration of their secretion by changes in diet, stress and other physiological perturbations. The regulation of their secretion is obviously very complex and poorly understood.

Insulin and glucagon play central roles in maintaining normal blood glucose concentrations and in increasing blood glucose concentrations in emergencies. Insulin and glucagon concentrations are greatest two to four hr after feeding (Figure 1) (9) and both decrease with starvation. The elevated insulin values after feeding participates in directing absorbed amino acids and acetate into peripheral tissues. A concomitant elevated glucagon concentration may be necessary as a gluconeogenic stimulus to prevent insulin hypoglycemia (22, 29). Consequently, it is at this time that glucose production is greatest (Figure 1) (18). During starvation, since dietary glucogenic substrates are less available, a lower glucagon level may reduce the activity of the gluconeogenic machinery. Absence of insulin would result in a net movement of amino acids for muscle and glycerol from adipose tissue lipolysis to the liver for use in glucose synthesis.

Hyperglycemia is a normal response to stress. Depressed insulin concentrations appear to be important (33) in attaining this hyperglycemia. In addition, elevated glucagon concentrations probably are vital in increasing hepatic glucose output.

In conclusion, insulin and glucagon play important roles in regulating ruminant metabolism, including hepatic gluconeogenesis. Insulin appears to be primarily involved in regulation at peripheral sites, specifically muscle and adipose tissue. Glucagon, on the other hand, appears to direct its action primarily at the liver to increase glucose production.

SUMMARY

Insulin and glucagon play central roles in maintaining normal blood glucose concentrations. In addition, they are important in the hyperglycemic response to stress.

Insulin, by promoting movement of glucose, acetate and amino acids into peripheral tissues, may be considered a storage hormone. Thus, the net effect of increased protein synthesis and lipogenesis in the long run is anabolic. Glucagon, on the other hand, is energy mobilizing. It increases hepatic glucose output and lipolysis. Since amino acids are used in gluconeogenesis, glucagon, by enhancing hepatic uptake of amino acids, has a net effect of reducing amino acids available for nonhepatic tissues. In the long term, then, it is catabolic.

The secretion of insulin and glucagon is influenced in many ways. Volatile fatty acids appear to be more potent than glucose with respect to stimulating insulin secretion. They also stimulate glucagon secretion. Amino acids are also important stimulators of their secretion. These metabolites, primarily of gastrointestinal origin, with gastrointestinal hormones, may be important modifiers of pancreatic endocrine secretion in order to adjust to changes in diet or energy intake. The autonomic nervous system also is implicated in regulation of insulin and glucagon secretion.

RÉSUMÉ

L'insuline et le glucagon jouent un rôle capital dans le maintien de la teneur normale du sang en glucose. Ils revêtent de plus une importance dans la réponse hyperglycémique au stress. Le fait que l'insuline favorise le mouvement du glucose, de l'acétate et des acides aminés vers les tissus périphériques, nous permet de la considérer comme une hormone d'entreposage. C'est ainsi, qu'à la longue, l'effet net d'une augmentation de la synthèse des protéines et de la lipogénèse se révèle anabolique. Par ailleurs, le glucagon mobilise l'énergie. Il augmente la libération du glucose par le foie et la lipolyse. Comme la glyconéogénèse implique l'utilisation d'acides aminés, le glucagon, en permettant au foie de capter une plus grande quantité d'acides aminés, possède un effet net sur la réduction de leur disponibilité pour les tissue autres que le foie. Le glucagon exerce donc, à la longue, un effet catabolique.

La sécrétion de l'insuline et du glucagon est sujette à plusieurs influences. Les acides gras

volatils semblent plus puissants que le glucose, en ce qui concerne la stimulation de la sécrétion d'insuline; ils stimulent aussi la sécrétion de glucagon. Les acides aminés représentent également des stimulants importants de la sécrétion de ces deux hormones. Ces métabolites qui proviennent surtout du tube gastro-intestinal pourraient, avec les hormones gastrointestinales, constituer d'importants modificateurs de la sécrétion pancréatique endocrine, de façon à ajuster les changements dans la diète ou l'absorption d'énergie. Le système nerveux autonome participe aussi à la régulation de la sécrétion de l'insuline et du glucagon.

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BOOK REVIEW

Laboratory Anatomy of the Cat. Sixth Edition. Robert B. Chiasson and Ernest S. Booth. Published by Burns & McEachern Limited, Don Mills, Ontario. 1977. 95 pages. Price $4.50.

This book is one of a series, and exactly fulfils its title. It deals with the basic laboratory approach to structure rather than taking a clinical view. The material is arranged by systems, with a chapter on each one.

The section on osteology has good, clear, well-labelled drawings, and the text is easy to understand. Much the same applies to myology, and together these chapters take up half of the book. Although the illustrations of musculature are good, they deliberately omit all vessels and nerves, so relationship of these systems to each other is not apparent. The tables which list all of the muscles together with the origin, insertion, and action of each would be most useful for students. The section in other systems, respiratory, reproductive, digestive, etc., cover the basic structures and are quite straightforward but not detailed.

This book is written for high school students, and at that level is very good, but comparisons are made with human structure, and terms such as hand, wrist, knee are still used as applied to the feline. The vocabulary is not always technical. However, there is a list of references for suggested reading at the end of each chapter, and these are probably of much use to the practitioner, since many are from scientific journals such as the American Journal of Veterinary Research. There is also an appendix which is definitely useful clinically, giving the ages at which major epiphyses unite with the shaft of a given bone, and the age at which permanent teeth erupt. Tables of linear measurement and weight of body parts are also an asset. *V. DeKleer.*